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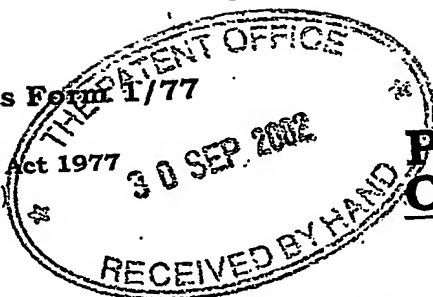
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Dated

*P. Mahoney*  
11 July 2003

Patents Form 1/77

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The  
**Patent  
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10/526760  
PCT/EP03/10175  
010CT02 E752023-1 D00524  
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1/77

**Request for grant of a patent**  
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The Patent Office  
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1. Your reference 4-32698P1

2. 30 SEP 2002

3. 0222617.3

Full name, address and postcode of the  
or of each applicant  
(underline all surnames)

NOVARTIS AG  
LICHTSTRASSE 35  
4056 BASEL  
SWITZERLAND

Patent ADP number (if you know it)

If the applicant is a corporate body,  
give the country/state of its  
incorporation

SWITZERLAND

7125487005

4. Title of invention Organic compounds

5. Name of your agent (if you have one)  
"Address for service" in the United  
Kingdom to which all correspondence  
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UK Limited  
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Country	Priority application number (if you know it)	Date of filing (day/month/year)
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

Yes

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
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(see note (d))

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Description 13

Claim(s) 2

Abstract DMC

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Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents  
(please specify)

11. I/We request the grant of a patent on the basis of this application

Signature

Date

B.A. Yorke & Co.

B.A. Yorke & Co.

30 September 2002

12. Name and daytime telephone number of person to contact in the United Kingdom  
Mrs. E. Cheetham  
020 8560 5847

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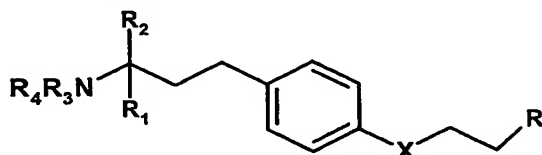
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Organic Compounds

The present invention relates to amino-propanol derivatives, process for their production, their uses and pharmaceutical compositions containing them.

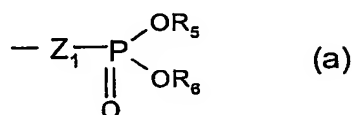
More particularly, the invention provides a compound of formula I



wherein

R<sub>1</sub> is methyl; ethyl; or (CH<sub>2</sub>)<sub>n</sub>-OH wherein n is 1 to 5;

R<sub>2</sub> is Z-X<sub>1</sub> wherein Z is CH<sub>2</sub>, CHF or CF<sub>2</sub> and X<sub>1</sub> is OH or a residue of formula (a)



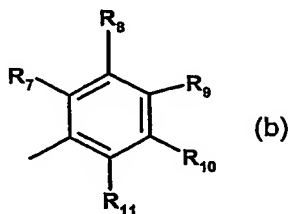
wherein Z<sub>1</sub> is a direct bond, CH<sub>2</sub>, CHF, CF<sub>2</sub> or O, and each of R<sub>5</sub> and R<sub>6</sub>,

independently, is H or C<sub>1-4</sub> alkyl optionally substituted by 1, 2 or 3 halogen atoms; and

each of R<sub>3</sub> and R<sub>4</sub>, independently, is H; C<sub>1-4</sub>alkyl optionally substituted by 1, 2 or 3 halogen atoms; or acyl;

X is O; CH<sub>2</sub>; or C=O; and

R is a residue of formula (b)



wherein each of R<sub>7</sub> to R<sub>11</sub>, independently, is H; Cl; Br; F; CN; CF<sub>3</sub>; OCF<sub>3</sub>; OCHF<sub>2</sub>;

C<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkoxy; C<sub>3-6</sub>cycloalkyl; C<sub>3-6</sub>cycloalkoxy; acyl; or optionally substituted

phenyl; or R<sub>9</sub> and R<sub>10</sub> form together 3,4-(-OCH<sub>2</sub>O-); or

(R<sub>7</sub> and R<sub>8</sub>) or (R<sub>8</sub> and R<sub>9</sub>) together with the carbon atoms to which they are attached, form a fused cyclic or heterocyclic ring and the remaining R<sub>9</sub> to R<sub>11</sub> or R<sub>7</sub> and R<sub>10</sub> and R<sub>11</sub>, respectively, are as defined above; or

$\alpha$ - or  $\beta$ -naphthyl optionally substituted by one to 5 substituents as defined above for  $R_7$  to  $R_{11}$ ;

in free form or in salt form.

Alkyl or alkyl moiety may be straight or branched chain, e.g. methyl, ethyl, propyl, iso-propyl or butyl. Cycloalkyl may be e.g. cyclopropyl. Cycloalkoxy may be e.g. cyclopropoxy.

Acyl may be a residue  $R-CO$  wherein  $R$  is  $C_{1-6}$ alkyl,  $C_{3-6}$ cycloalkyl, phenyl or phenyl $C_{1-4}$ alkyl. When the phenyl as  $R_7$ ,  $R_8$ ,  $R_9$ ,  $R_{10}$ , or  $R_{11}$  is substituted, it may be substituted by one to five substituents as defined above for  $R_7$  to  $R_{11}$ , except phenyl.

Examples of saturated or unsaturated heterocyclic rings formed by ( $R_7$  and  $R_8$ ) or ( $R_8$  and  $R_9$ ) together with the carbon atoms to which they are attached include e.g. rings containing 1 or 2 heteroatoms selected from N, O or S, e.g. thienyl, furyl, pyrrolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyrazolyl, dehydrodioxolane or dehydrodioxane.

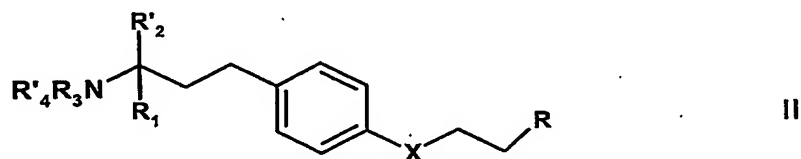
Examples of cyclic rings formed by ( $R_7$  and  $R_8$ ) or ( $R_8$  and  $R_9$ ) together with the carbon atoms to which they are attached include e.g. cyclopentene, cyclohexene.

Compounds of formula I may exist in free form or in salt form, e.g. addition salts with e.g. inorganic acids, such as hydrochloride, hydrobromide or sulfate, salts with organic acids, such as acetate, fumarate, maleate, benzoate, citrate, malate, methanesulfonate or benzenesulfonate salts; when  $R_5$  or  $R_6$  is H, the phosphate group may also be present in salt form, e.g. an ammonium salt or salts with metals such as sodium, potassium, calcium, zinc or magnesium, or a mixture thereof. Compounds of formula I and their salts, in hydrate or solvate form are also part of the invention.

When the compounds of formula I have asymmetric centers in the molecule, various optical isomers are obtained. The present invention also encompasses enantiomers, racemates, diastereoisomers and mixtures thereof. For example, the central carbon atom bearing  $R_1$ ,  $R_2$  and  $NR_3R_4$  may have the R or S configuration. Compounds having the R configuration at this central carbon atom are preferred; however, the S configuration is preferred for compounds of formula I wherein  $R_1$  is  $-(CH_2)_2-OH$ . Moreover, when the compounds of formula I include geometric isomers, the present invention embraces cis-compounds, trans-compounds and mixtures thereof. Similar considerations apply in relation to starting materials exhibiting asymmetric carbon atoms or unsaturated bonds as mentioned above, e.g. compounds of formula II, III or IV as indicated below.

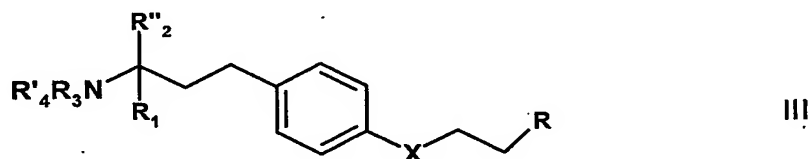
The present invention also includes a process for the preparation of a compound of formula I which process comprises

a) for a compound of formula I wherein  $R_2$  is  $Z-X_1$ ,  $X_1$  being OH, removing the protecting group present in a compound of formula II

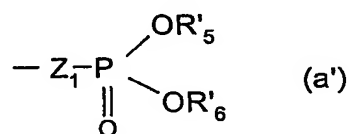


wherein X, R,  $R_1$  and  $R_3$  are as defined above,  $R'_2$  is  $Z-X_1$  wherein  $X_1$  is OH and  $R'_4$  is an amino protecting group, or

b) for a compound of formula I wherein  $R_2$  is  $Z-X_1$ ,  $X_1$  being a residue of formula (a), removing the protecting groups present in a compound of formula III



wherein X, R,  $R_1$ ,  $R_3$  and  $R'_4$  are as defined above, and  $R''_2$  is  $Z-X_1$  wherein  $X_1$  is a residue of formula (a')



wherein  $Z_1$  is as defined above and each of  $R'_5$  or  $R'_6$  is a hydrolysable or hydrogenolysable group or  $R'_5$  and  $R'_6$  form together a divalent bridging residue optionally fused to a ring (e.g. benzene ring),

and, where required, converting the compounds of formula I obtained in free form into the desired salt form, or vice versa.

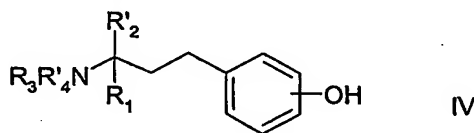
Process step a) may be carried out in accordance with methods known in the art. The removal of the amino protecting groups may conveniently be performed according to methods known in the art, e.g. by hydrolysis, e.g. in an acidic medium, for example using hydrochloric acid. Examples of protecting groups for amino groups are e.g. as disclosed in "Protective Groups in Organic Synthesis" T.W. Greene, J.Wiley & Sons NY, 2<sup>nd</sup> ed., chapter

7, 1991, and references therein, e.g. benzyl, p-methoxybenzyl, methoxymethyl, tetrahydropyranyl, trialkylsilyl, acyl, tert.-butoxy-carbonyl, benzyloxycarbonyl, 9-fluorenyl methoxy carbonyl, trifluoroacetyl, and the like.

In the residue of formula (a'), each of R'<sub>5</sub> and R'<sub>6</sub> may have the significance of e.g. phenyl or benzyl or form together a cyclic system such as in 1,5-dihydro-2,4,3-benzodioxaphosphin.

Process step (b) may be performed according to methods known in the art, e.g. by hydrolysis, e.g. in a basic medium when R'<sub>5</sub> and R'<sub>6</sub> are each a hydrolysable group, for example using a hydroxide such as barium hydroxide. It may also be performed by hydrogenolysis, e.g. in the presence of a catalyst, e.g. Pd/C, followed by hydrolysis, e.g. in an acidic medium, for example HCl. Compounds of formulae II and III, used as starting materials, and salts thereof are also novel and form part of the invention.

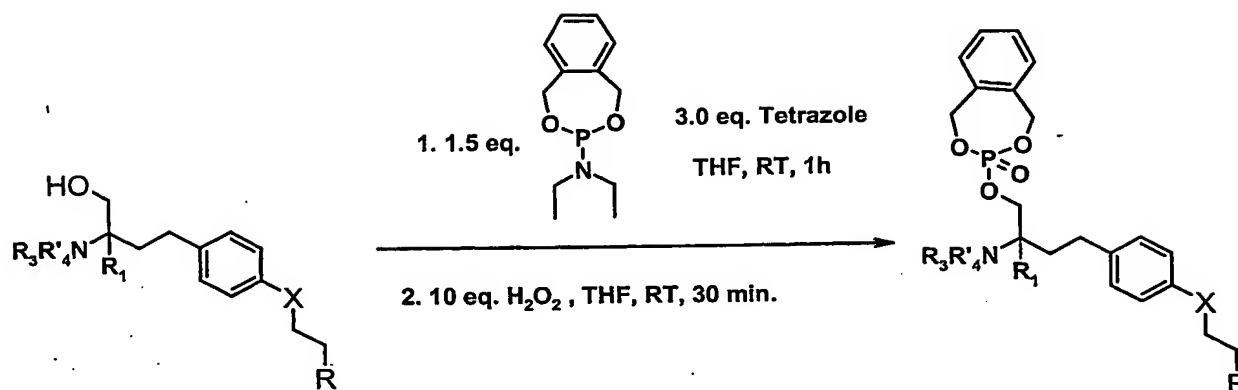
The present invention also includes a process for the preparation of a compound of formula II which process comprises alkylating a compound of formula IV



wherein R<sub>1</sub>, R'<sub>2</sub>, R<sub>3</sub> and R'<sub>4</sub> are as defined above, to introduce the desired residue X-CH<sub>2</sub>-CH<sub>2</sub>-R.

Alkylation of the compounds of formula IV may be performed according to methods known in the art, e.g. by nucleophilic substitution, e.g. by reaction of a compound of formula IV with an alkylating agent of formula R-CH<sub>2</sub>CH<sub>2</sub>-X<sub>3</sub> wherein R is as defined above and X<sub>3</sub> is mesylate, tosylate, triflate, nosylate or an halogen, e.g. chloride, bromide or iodide. The alkylation may also be carried out by following the Mitsunobu protocol (e.g. as disclosed in Hughes, Organic Preparations and Procedures International 28, 127-64, 1996 or D.L. Hughes, Org. React. 42, 335, 1992), in solution or on solid phase support synthesis, e.g. by attaching the compound of formula IV to a resin. Alternatively, either triphenylphosphine or e.g. diethyl azocarboxylate bound to a resin, e.g. polystyrene, can be used.

Compounds of formula III wherein R'<sub>5</sub> and R'<sub>6</sub> form a cyclic system, may be prepared as follows:



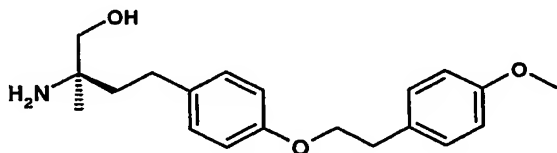
wherein X, R, R<sub>1</sub>, R<sub>3</sub> and R'<sub>4</sub> are as defined above.

Insofar as the production of the starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as disclosed in the Examples hereinafter.

The following Examples are illustrative of the invention. Melting points are uncorrected.

RT	=	room temperature
DCM	=	dichloromethane
Bn	=	benzyl
THF	=	tetrahydrofuran
DMF	=	dimethylformamide
MTBE	=	methyl tert.-butyl ether

**Example 1: (R)-2-Amino-4-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-2-methyl-butan-1-ol**



a) ((R)-3-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-1-hydroxymethyl-1-methyl-propyl)-carbamic acid tert-butyl ester:

To a solution of phenol A (0.1 mol) and methanesulfonic acid phenethyl ester (0.1 mol) in ethanol (500 ml) is added potassium carbonate (0.3 mol). The suspension is stirred at 70°C for 16 h and cooled to RT. After filtration, the solvent is evaporated and the crude residue

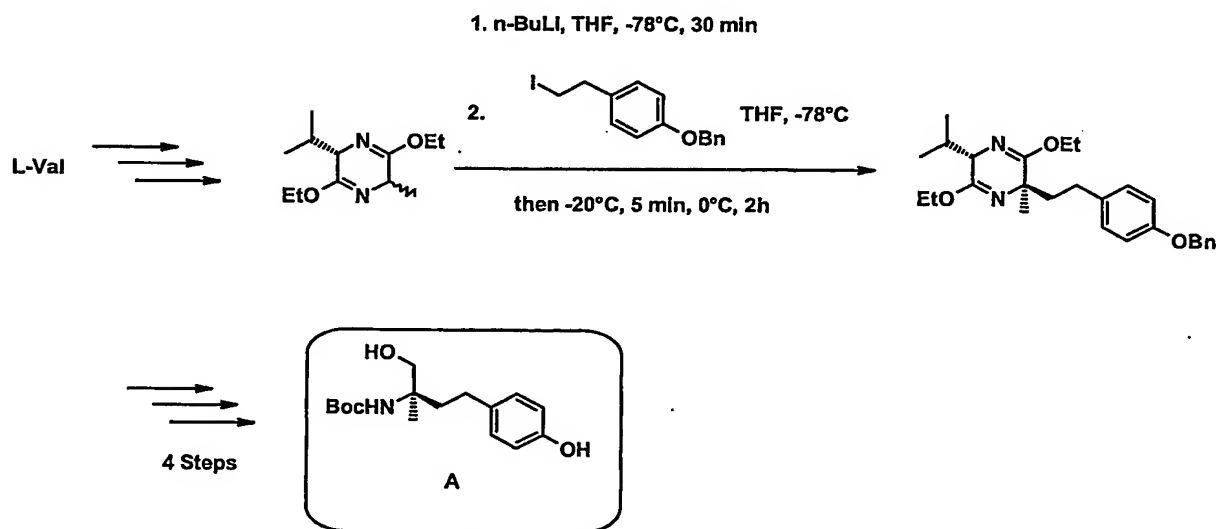


purified by chromatography using silica gel and  $\text{CH}_2\text{Cl}_2/\text{MeOH} = 20/1$  to give the alkylated product as white crystalline solid.

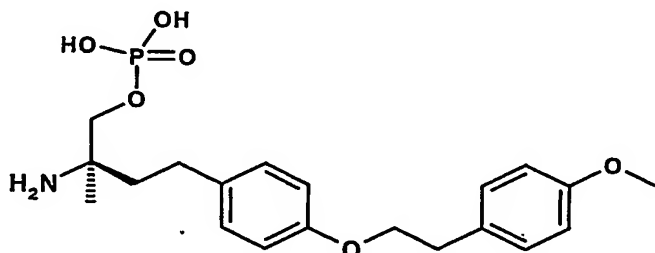
b) *(R)*-2-Amino-4-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-2-methyl-butan-1-ol

The compound of step a) (0.01 mol) is dissolved in dioxane (25ml). After adding 5N HCl (25 ml), the mixture is left standing at RT for 6h. The solvent is carefully removed by lyophilisation to deliver the desired product.

The phenolic building block *tert*-Butyl [(*R*)-1-hydroxymethyl-3-(4-hydroxy-phenyl)-1-methyl-propyl]-carbamate used in the starting material may be prepared in a six step sequence starting from D-Val-Gly-Schöllkopf reagent. The desired product can be obtained enantioselectively.



**Example 2:** Phosphoric acid mono-((*R*)-2-amino-4-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-2-methyl-butyl) ester



a) *tert*-butyl {(R)-2-Methyl-2-(3-oxo-1,5-dihydro-3 $\lambda^5$ -benzo[e][1,3,2]dioxaphosphhepin-3-yloxy)-4-[4-(methoxy)-phenyl]-but-2-yl}-carbamate

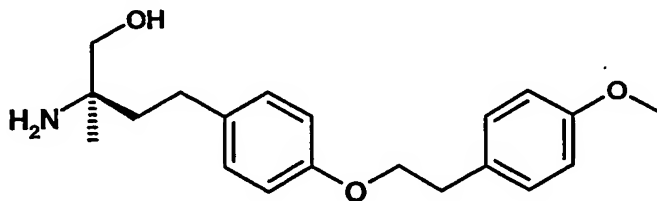
To a solution of *tert*-Butyl {(R)-1-hydroxy-2-methyl-4-[4-(methoxy)-phenyl]-but-2-yl}-carbamate (0.088 mmol, Example 1 a) and tetrazole (18 mg, 0.26 mmol, 3 eq., recrystallized from toluene) in dry THF (1 mL) is added 3-diethylamino-1,5-dihydro-benzo[e][1,3,2]dioxaphosphhepine (32  $\mu$ L, 0.13 mmol, 1.5 eq.). The reaction mixture is stirred under argon at RT for 3h. Then, hydrogen peroxide (30%, 90  $\mu$ L, 0.88, 10 eq.) is injected at 0°C with vigorous stirring. The reaction mixture is stirred for further 30 min, followed by addition of saturated sodium thiosulfate solution (1 mL). The organic layer is separated and the aqueous phase is extracted with ether (3 x 1 mL). The combined organic extracts are washed with brine, dried over magnesium sulfate, and evaporated to dryness. The crude material is purified by flash chromatography (MTBE/Hexane 1:1) to afford colorless crystals.

b) mono-((R)-2-Amino-4-{4-[2-(4-methoxy-phenyl)-ethoxy]-phenyl}-2-methyl-butyl) phosphate

To a solution of compound of step a) above (0.05 mmol) in methanol is added 10% Pd/C (50 mg). The suspension is purged with nitrogen and then hydrogenated at atmospheric pressure with gentle stirring for 2h. After this, the catalyst is removed by filtration through Celite. The filtrate is evaporated to dryness to give a colorless resin. The material is re-dissolved in dioxane (0.75 mL) and 4 M HCl in dioxane (0.25 mL) is added. After stirring for 2h the slightly turbid solution is evaporated. The colorless semi-solid residue is sonicated with dry ether (5 mL) to give a colorless precipitate. The solid is filtered off, washed with dry ether and vacuum dried to afford a colorless powder.

Compounds of Examples 3, 5 and 7 are prepared in accordance with the procedure of Example 1, using appropriate mesylates. Purification takes place after the alkylation step.

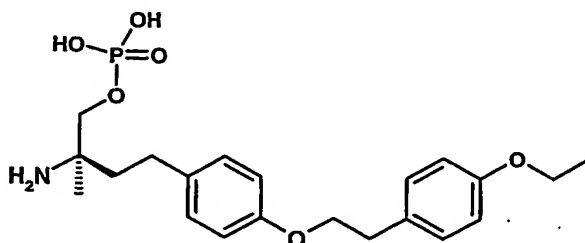
**Example 3:** (R)-2-Amino-4-{4-[2-(4-ethoxy-phenyl)-ethoxy]-phenyl}-2-methyl-butan-1-ol



MS (ESI+): 344 (MH<sup>+</sup>)

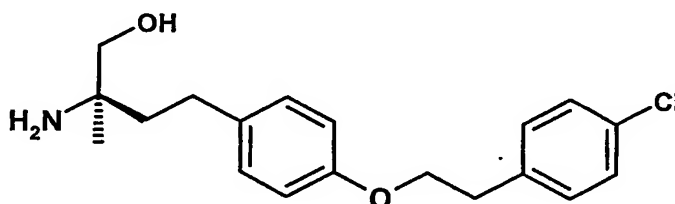
Compounds of Examples 4, 6 and 8 are prepared in accordance with the procedure of Example 2, using the appropriate starting materials.

**Example 4:** Phosphoric acid mono-((R)-2-amino-4-{4-[2-(4-ethoxy-phenyl)-ethoxy]-phenyl}-2-methyl-butyl) ester



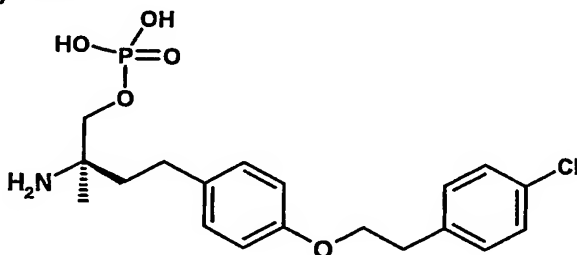
MS (ESI<sup>-</sup>): 422 (M-H<sup>-</sup>)

**Example 5:** (R)-2-Amino-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-methyl-butan-1-ol



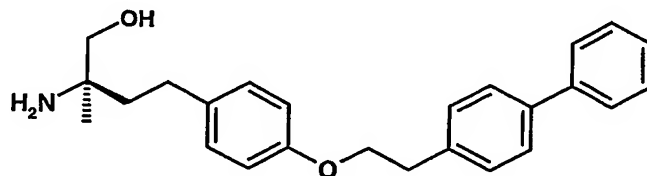
MS (ESI<sup>+</sup>): 334 (MH<sup>+</sup>)

**Example 6:** Phosphoric acid mono-((R)-2-Amino-4-{4-[2-(4-chloro-phenyl)-ethoxy]-phenyl}-2-methyl-butyl) ester



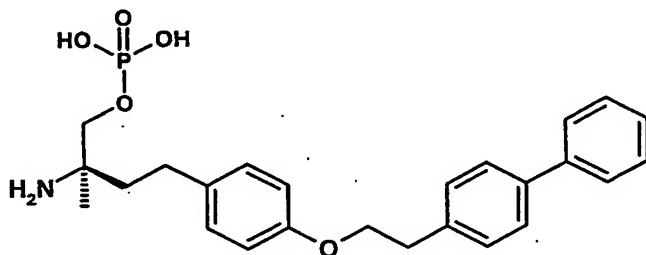
MS (ESI<sup>-</sup>): 412 (M-H<sup>-</sup>)

**Example 7:** (R)-2-Amino-4-[4-(2-biphenyl-4-yl-ethoxy)-phenyl]-2-methyl-butan-1-ol



MS (ESI<sup>+</sup>): 376 (MH<sup>+</sup>)

**Example 8: mono-{(R)-2-amino-4-[4-(2-biphenyl-4-yl-ethoxy)-phenyl]-2-methyl-butyl} phosphate**



MS (ESI-): 454 (M-H<sup>-</sup>)

The compounds of formula I in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties, e.g. lymphocyte recirculation modulating properties, e.g. as indicated in in vitro and in vivo tests and are therefore indicated for therapy.

**A. In vitro**

The compounds of formula I have binding affinity to individual human S1P receptors as determined in following assays:

**Sphingosine-1-phosphate (S1P) receptor profiling**

Agonist activities of compounds are tested on the human S1P receptors EDG-1 (S1P<sub>1</sub>), EDG-3 (S1P<sub>3</sub>), EDG-5 (S1P<sub>2</sub>), EDG-6 (S1P<sub>4</sub>) and EDG-8 (S1P<sub>5</sub>). Functional receptor activation is assessed by quantifying compound induced GTP [ $\gamma$ -<sup>35</sup>S] binding to membrane protein prepared from transfected CHO or RH7777 cells stably expressing the appropriate human S1P receptor. The assay technology used is SPA (scintillation proximity based assay). Briefly, DMSO dissolved compounds are serially diluted and added to SPA- bead (Amersham-Pharmacia) immobilised S1P receptor expressing membrane protein (10-20  $\mu$ g/well) in the presence of 50 mM Hepes, 100 mM NaCl, 10 mM MgCl<sub>2</sub>, 10  $\mu$ M GDP, 0.1% fat free BSA and 0.2 nM GTP [ $\gamma$ -<sup>35</sup>S] (1200 Ci/mmol). After incubation in 96 well microtiterplates at RT for 120 min, unbound GTP [ $\gamma$ -<sup>35</sup>S] is separated by a centrifugation step. Luminescence of SPA beads triggered by membrane bound GTP [ $\gamma$ -<sup>35</sup>S] is quantified with a TOPcount plate reader (Packard). EC<sub>50</sub>s are calculated using standard curve fitting software.

Example	S1P <sub>1</sub> EC <sub>50</sub> [nM]	S1P <sub>2</sub> EC <sub>50</sub> [nM]	S1P <sub>3</sub> EC <sub>50</sub> [nM]	S1P <sub>4</sub> EC <sub>50</sub> [nM]	S1P <sub>5</sub> EC <sub>50</sub> [nM]
2	16 Agon.	> 10000 -	248 Agon.	5330 Antag	16.4 Agon.
8	0.21 Agon.	> 10000 -	25 Agon.	7 Antag	6.4 Agon.

#### B. In vivo: Blood Lymphocyte Depletion

A compound of formula I or the vehicle is administered orally by gavage to rats. Tail blood for hematological monitoring is obtained on day -1 to give the baseline individual values, and at 2, 6, 24, 48 and 72 hours after application. In this assay, the compounds of formula I deplete peripheral blood lymphocytes when administered at a dose of 0.03 to 3 mg/kg. For example, following results are obtained: depletion of peripheral blood lymphocytes by more than 50%

Example 1: 0.07 mg/kg p.o. after 6h, 0.05 mg/kg p.o. after 24h

Example 3: 0.03 mg/kg p.o. after 6h, 0.04 mg/kg p.o. after 24h

Example 5: 0.8 mg/kg p.o. after 6h, 0.7 mg/kg p.o. after 24h

Example 7: 0.1 mg/kg p.o. after 6h, 0.03 mg/kg p.o. after 24h

The compounds of formula I are, therefore, useful in the treatment and/or prevention of diseases or disorders mediated by lymphocytes interactions, e.g. in transplantation, such as acute or chronic rejection of cell, tissue or organ allo- or xenografts or delayed graft function, graft versus host disease, autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus, hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, vasculitis, pernicious anemia, Sjogren syndrome, uveitis, psoriasis, Graves ophthalmopathy, alopecia areata and others, allergic diseases, e.g. allergic asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, allergic contact dermatitis, inflammatory diseases optionally with underlying aberrant reactions, e.g. inflammatory bowel disease, Crohn's disease or ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye disease, keratoconjunctivitis, myocarditis or hepatitis, ischemia/reperfusion injury, e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, traumatic shock, cancer, e.g. breast cancer, T cell lymphomas or T cell leukemias, infectious diseases, e.g. toxic shock (e.g. superantigen induced), septic shock,

adult respiratory distress syndrome or viral infections, e.g. AIDS, viral hepatitis, chronic bacterial infection, or senile dementia. Examples of cell, tissue or solid organ transplants include e.g. pancreatic islets, stem cells, bone marrow, corneal tissue, neuronal tissue, heart, lung, combined heart-lung, kidney, liver, bowel, pancreas, trachea or oesophagus. For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired.

In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 100 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 0.1 to 50 mg active ingredient.

The compounds of formula I may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of formula I in free form or in pharmaceutically acceptable salt form in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

The compounds of formula I may be administered in free form or in pharmaceutically acceptable salt form e.g. as indicated above. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

- 1.1 A method for preventing or treating disorders or diseases mediated by lymphocytes, e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
- 1.2 A method for preventing or treating acute or chronic transplant rejection or T-cell mediated inflammatory or autoimmune diseases, e.g. as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

2. A compound of formula I, in free form or in a pharmaceutically acceptable salt form for use as a pharmaceutical, e.g. in any of the methods as indicated under 1.1 or 1.2 above.
3. A pharmaceutical composition, e.g. for use in any of the methods as in 1.1 or 1.2 above comprising a compound of formula I in free form or pharmaceutically acceptable salt form in association with a pharmaceutically acceptable diluent or carrier therefor.
4. A compound of formula I or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in any of the method as in 1.1 or 1.2 above.

The compounds of formula I may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. immunosuppressive or immunomodulating agents or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, or a chemotherapeutic agent, e.g. a malignant cell anti-proliferative agent. For example, the compounds of formula I may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; a mTOR inhibitor, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779, ABT578 or AP23573; an ascomycin having immunosuppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40, CD45, CD58, CD80, CD86 or their ligands; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or a chemotherapeutic agent, e.g. paclitaxel, gemcitabine, cisplatinum, doxorubicin or 5-fluorouracil; or an anti-infectious agent.

Where the compounds of formula I are administered in conjunction with other immunosuppressive / immunomodulatory, anti-inflammatory, chemotherapeutic or anti-infectious therapy, dosages of the co-administered immunosuppressant, immunomodulatory,

anti-inflammatory, chemotherapeutic or anti-infectious compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth. In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a compound of formula I and at least a second drug substance, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic drug, e.g. as indicated above.
6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a compound of formula I as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory, chemotherapeutic or anti-infectious agent. The kit may comprise instructions for its administration.

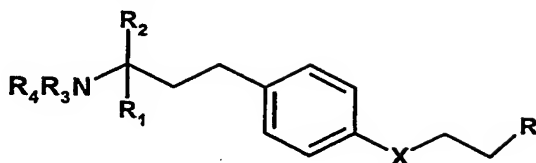
The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.



## CLAIMS

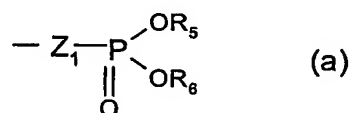
1. A compound of formula I



wherein

$R_1$  is methyl; ethyl; or  $(CH_2)_n-OH$  wherein  $n$  is 1 to 5;

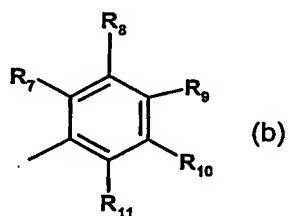
$R_2$  is  $Z-X_1$  wherein  $Z$  is  $CH_2$ ,  $CHF$  or  $CF_2$  and  $X_1$  is  $OH$  or a residue of formula (a)



wherein  $Z_1$  is a direct bond,  $CH_2$ ,  $CHF$ ,  $CF_2$  or  $O$ , and each of  $R_5$  and  $R_6$ , independently, is  $H$  or  $C_{1-4}$  alkyl optionally substituted by 1, 2 or 3 halogen atoms; and each of  $R_3$  and  $R_4$ , independently, is  $H$ ;  $C_{1-4}$ alkyl optionally substituted by 1, 2 or 3 halogen atoms; or acyl;

$X$  is  $O$ ;  $CH_2$ ; or  $C=O$ ; and

$R$  is a residue of formula (b)



wherein each of  $R_7$  to  $R_{11}$ , independently, is  $H$ ;  $Cl$ ;  $Br$ ;  $F$ ;  $CN$ ;  $CF_3$ ;  $OCF_3$ ;  $OCHF_2$ ;  $C_{1-6}$ alkyl;  $C_{1-6}$ alkoxy;  $C_{3-6}$ cycloalkyl;  $C_{3-6}$ cycloalkoxy; acyl; or optionally substituted phenyl; or  $R_9$  and  $R_{10}$  form together 3,4- $(-OCH_2O-)$ ; or

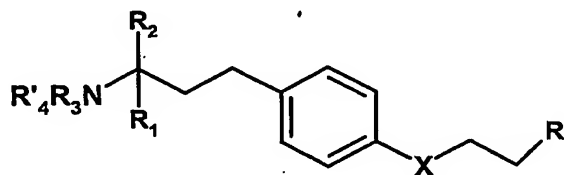
$(R_7$  and  $R_8)$  or  $(R_8$  and  $R_9)$  together with the carbon atoms to which they are attached, form a fused cyclic or heterocyclic ring and the remaining  $R_9$  to  $R_{11}$  or  $R_7$  and  $R_{10}$  and  $R_{11}$ , respectively, are as defined above; or

$\alpha$ - or  $\beta$ -naphthyl optionally substituted by one to 5 substituents as defined above for  $R_7$  to  $R_{11}$ ;

in free form or in salt form,

a process for its preparation, its use as a pharmaceutical, a pharmaceutical composition containing such a compound or a pharmaceutically acceptable salt thereof, a method of treatment or prevention using such a compound or a pharmaceutically acceptable salt thereof, or a pharmaceutical combination comprising such a compound or a pharmaceutically acceptable salt thereof, substantially as herein defined and/or described.

2. A compound of formula



wherein X, R, R<sub>1</sub> to R<sub>3</sub> and R'<sub>4</sub> are as defined above,

or a salt thereof,

and a process for its preparation, substantially as hereinbefore defined and/or described.

PCT Application  
**EP0310175**

